PERSPECTIVES

Lactate doesn't necessarily cause fatigue: why are we surprised?

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Everyone *knows* that lactic acidosis causes fatigue. But is it in fact true that the fatigue associated with severe exercise is caused by lactate? And, moreover, how did this received opinion come to be? In many instances our teachers instructed us in this fact as they challenged us to read classical works of the progenitors of biochemistry and muscle physiology. Subsequently, we faithfully transferred this knowledge to our students. Routinely, the association between acidosis and fatigue is reinforced in our minds and psyches by sports journalists and commentators who reiterate what we previously conveyed through our teachings and writings. However, with the results of Nielsen *et al.* (2001) reported in this issue of *The Journal of Physiology*, as well as other recent findings, we need to reconsider the appropriateness of this Homeric transfer of knowledge concerning lactic acidosis and muscle fatigue.

Since the work of Fletcher & Hopkins (1907), Meyerhof (1920) and A. V. Hill (1932) it has been known that isolated muscles made to contract until fatigue accumulate lactic acid. Further, it was observed that if oxygen was present in recovery, lactic acid level declined while glycogen concentration and contractile function were restored (Meyerhof, 1920; Hill, 1932). Hence, the associations between oxygen insufficiency, lactic acidosis and disrupted function have been presumed by physiologists and clinicians alike (Brooks, 1991; Wasserman & McIlroy, 1964).

More recently, beneficial effects of lactate anions in providing oxidizable substrate and gluconeogenic precursors, as well as in cell–cell signalling such as in glutamate-mediated synaptic transmission have been recognized (Brooks, 1991; Pellerin *et al.* 1998). Moreover, lactic acid (lactate and associated proton) clearance through oxidation and gluconeogenesis during human exercise has been thought to provide a beneficial, alkalizing, effect on blood pH (Brooks, 1991). Cell–cell and intracellular lactate transport across membrane barriers are now known to be facilitated by lactate transport proteins that co-transport lactate and hydrogen ions. Further, several lactate (monocarboxylate; MCT) transporter isoforms are expressed in different tissues and MCTs occupy specific cell domains (Price *et al.* 1998). Still, despite recognition of the beneficial effects of lactate production and exchange, popular concern persists over the consequences of hydrogen ion production and accumulation during exercise.

Given the results of Nielsen *et al.* (2001) we should relax a bit about the hazardous consequences of acidosis, but we need again to acknowledge that Nature is smarter, and things are more complex than we mortals imagine. Specifically, results of the paper of Nielsen *et al.* require us to once again reevaluate our notions of lactic acidosis and muscle fatigue. As elegantly described in their paper on electrically stimulated isolated rat soleus muscles, Nielsen and colleagues describe how contractions cause both lactic acidosis and loss of intracellular K^+ with accumulation of extracellular K^+ ($[K^+]_o$). In their experiments high $[K^+]_o$ led to loss of tetanic force. However, first with lactic acid, then with propionic and carbonic acids (from addition of high CO_2) Nielsen and colleagues observed that acidification counteracts the effects of elevated $[K^+]_o$ that are associated with muscle fatigue.

Certainly, repeated, high intensity contractions lead to muscle fatigue. Glycogenolysis and glycolysis can lead to lactic acidosis and disturbances to muscle and plasma pH. Furthermore, contractions also precipitate a variety of other disturbances to cell homeostasis including perturbations to energy charge and ion balances. Whether K^+ imbalances always, sometimes or hardly ever lead to fatigue during exercise *in vivo* is uncertain at this point. Certainly, muscles can be made to contract to fatigue *in vivo* without loss of the M-waves in EMG. However, isn't it interesting to observe, at least on muscles studied *in vitro*, that one consequence of repeated forceful muscle contraction (i.e. H^+ accumulation) offers a degree of protection against another consequence of contraction (i.e. increased $[K^+]_o$)? As we look forward to learning more about the role of potassium ion imbalance and lactic acidosis in muscle function in normal and pathological situations we are given cause to wonder how robust are other notions of physiology that we have long held.

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